REMARKS

Claims 28-49 are pending. Claim 28 was found to be allowable. In the present response to the final Office Action, claims 1-27 have been cancelled without prejudice or disclaimer, and new claims 29-48 drafted for ease of examination. Support for new Claims 29-48 derives from the specification and claims as originally filed. For example, the specification at page 48, line 27 states that the TNF- α variants can be purified or isolated. The specification at page 47, lines 5-28, discusses glycosylation of TNF- α proteins. Additionally, the specification at page 22, lines 6-13, discusses mixed trimers and various ratios of wild-type to variant monomers. Accordingly, the new claims do not present new matter and entry is proper.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 1, 2, 16, 17, 19-24 and 27 stand rejected under 35 U.S.C. § 112, first paragraph for lack of written description and enablement.

Claims 1, 2, 16, 17, 19-24 and 27 have been cancelled, however the Applicants address the rejection as it applies to new claims 29-49. The Examiner's position appears to be that claims disclosing variant TNF-α proteins need to reference a sequence. Applicants respectfully disagree.

In addressing the written description requirement under 35 U.S.C. § 112, as it applied to a genus of cDNAs, the Federal Circuit in University of *California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997), stated:

> A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling with the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. This is analogous to enablement of a genus under Section 112, para. 1, by

> showing the enablement of a representative number of species within the genus. *See Angstadt*, 537 F.2d at 502-03 (deciding that applicants "are *not* required to disclose *every* species encompassed by their claims their claims even in an unpredictable art and that the disclosure of forty working examples sufficiently described subject matter of claims directed to a generic process) . . . See also *In re Grimme*, 274 F.2d, 949, 952 ("[I]t has been consistently held that the naming of one member of such a group is not, in itself, a proper basis for a claims to the entire group. However, it may not be necessary to enumerate a plurality of species if a genus is sufficiently identified in an application by other appropriate language.").

Applicants respectfully submit that the specification provides written description support and enables a genus of variant TNF-α proteins as disclosed in new claims 29-49. First, the specification recites more than 70 variant TNF-α proteins that have been generated using the methods described therein. Second, the specification provides experimental data for 11 variant TNF-α proteins that demonstrates that the variant proteins are capable of forming trimers that are incapable of activating receptor signaling. Finally, the specification and claims as filed describe structural features common to the members of the genus. For example, the specification at page 25 discloses that the antigenic profile of the variant proteins should be similar to the wild-type protein. The specification at page 22, discloses that the variant proteins should be capable of interacting with wild type proteins to form trimers.

Accordingly, Applicants respectfully submit that the specification enumerates a number of species to provide the proper basis for claims to the entire genus of variant TNF-α proteins and request withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 19-26 are rejected under 35 U.S.C. § 112, second paragraph, for not providing the species information of the TNF-α protein used in the instant invention.

Claim 21 is rejected under 35 U.S.C. § 112, second paragraph, for referring to a single protein rather than a monomer of a TNF-α trimer. Claim 21 has been cancelled and thus the rejection is moot. Applicants respectfully submit that the rejection does not apply to new claims 29-45, because new claims 29-45 refer to monomers.

Claim 27 is rejected under 35 U.S.C. § 112, second paragraph, because it is unclear as to how to determine the nature of the amino acid substitution. Claim 21 has been cancelled and thus the rejection is moot. Applicants respectfully submit that the rejection does not apply to new claims 29-49, because the new claims 29-49 disclose a reference sequence for the amino acid substitutions.

Claims 19-24 are rejected under 35 U.S.C. § 112, second paragraph, for not providing a wild type species for a TNF-α protein. Claims 19-24 has been cancelled and thus the rejection is moot. Applicants respectfully submit that the rejection does not apply to new claims 29-49, because a sequence for the wild-type TNF-α protein has been provided.

Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 112, second paragraph.

Rejections under 35 U.S.C. § 102

Claims 1-2, 14-15 and 19 remain rejected under 35 U.S.C. § 102(b) as being anticipated by Banner *et al.*, U.S. Patent No. 5, 597,899. The rejection is moot as applied to cancelled claims 1-2, 14-15 and 19, and traversed as applied to new claims 29-49.

Banner *et al.*, discloses human TNF-α muteins having higher binding affinity for human p75-TNF receptor than for human p55-TNF receptor. However, there is no disclosure in Banner regarding compositions comprising: a) isolated, mixed trimers comprising monomers with different amino acid sequences (claims 29-39, and 43); b) glycolsylated homo- or mixed-trimers (claims 40-42 and 45); or c) variants with the disclosed amino acid changes at positions 21, 31, 32, 35, 66, 111, 112, 115, 140, 144, and 146.

In contrast, new claims 29-49 are directed towards TNF-α trimers that can be: (1) mixed, (2) glycosylated mixed trimers; (3) glyosylated homo-trimers; and, (4) homo-trimers with the disclosed amino acid changes.

An anticipation rejection requires that a single reference expressly or inherently disclose each and every element of a claim. *In re Paulsen*, 31 USPQ2d 1671, 1673 (Fed. Cir. 1994); MPEP § 2131 (citing *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989)). Additionally, the reference must enable and describe the claimed invention "sufficiently to have placed it in possession of a person of ordinary skill in the field of the invention." 31 USPQ2d at 1673. To be enabling, the reference must teach the skilled artisan how to make and use the full scope of the claimed invention without undue experimentation. See *Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997).

As can be seen from the above discussion, Banner *et al.*, does not disclose mixed trimers, glycosylated mixed trimers, glycosylated homo-trimers, or homo-trimers with the disclosed amino acid changes. Therefore, Banner *et al.* does not explicitly teach or

suggest each and every element of the claimed invention. Accordingly, Applicants respectfully request the Examiner to withdraw the rejection under 102(b).

Please direct further questions in connection with this Application to the undersigned at (415) 781-1989.

Respectfully submitted,

Dated: 6/22/04

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Filed under 37 C.F.R. § 1.34(a)

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